REMARKS

The Office Communication, mailed October 24, 2002, has been received and reviewed. Claims 1-3, 5, 7-10, 13 and 27-37 are pending. Claims 1-3, 5, 8-10, 13, 27-33 and 336-37 have been canceled without prejudice or disclaimer. Claim 7 has been amended. Basis for the amendment can be found, for example, in paragraph 27 of the specification. Claims 34, 35 have been amended accordingly. New claims 38-40 have been added. Basis for these claims can be found, for example, in paragraphs 28 and 29.

Claims 7, 34, 35 and 38-40 are currently pending.

I. Drawings

Black and white drawings are herewith submitted in a separate letter to the chief draftsperson.

II. 35 U.S.C. § 112, first paragraph

Claims 7-9, 30 and 34-37 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement commensurate with the claim scope.

Independent claim 7 has been amended to more definitely claim the present invention. The phrase "gene delivery vehicle" has been removed. Independent claim 7, as amended, and dependent claims 34-35 and 38-40, recite the use of a recombinant adenovirus to deliver the gene of interest. Thus, the gene delivery vehicle is defined in the claims.

The Office alleges that delivering a gene of interest to any recipient cell is not enabled. The claims have been amended to remove "delivering a gene of interest to a recipient cell." Furthermore, as acknowledged by the Examiner on page 6 of paper 10, the adenoviral gene-therapy vector is effective in rats having antibodies directed to an adenovirus of the same serotype. Intratumoral infejection was minimally affected and gene transfer to the liver and spleen was inhibited, but not abolished. This example was designed to test the ability of immunization to protect the liver and spleen, not as an example of how to treat the liver or spleen. A person of ordinary skill in the art, using the guidance of the specification, would utilize an administration route consistent with the tissue to be treated.

The Office also alleges that a dose for a second vector that is greater than the neutralizing antibody is not enabled. The claims have been amended to remove the dose of the second vector, greater than an amount which can be neutralized by the humoral response. The Office alleges that Havey *et al.* teaches that humoral response to Ad vectors is affected by the route of administration, but not the dose. The applicants submit that Harvey *et al.* demonstrates a decreased humoral antibody response to Ad_{GV}CFTR.10 vector administered to the respiratory epithelium of cystic fibrosis patients. The authors themselves postulate that the decreased immune response may be an effect of the cystic fibrosis. Specifically, "the airway epithelium of these individuals is covered by high quantities of mucopurulent secretions which could preclude efficient Ad-vector infection of the airway epithelial cells." Harvey *et al.* at page 6737, col. 2, last paragraph. The authors acknowledge that the decreased humoral response may be due to a decrease in the effective administration of immunizing virus. Thus, Harvey *et al.* is inapplicable to a humoral response to adenovirus, wherein the adenovirus is specifically introduced to generate an immune response in humans.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. 35 U.S.C. § 112, second paragraph

Claims 1-3, 5, 7-10, 13 and 27-37 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The claims were thought to be vague because the claims recite "essentially identical." Claims 1-3, 5, 8-10, 13 and 27-33 and 36-37 have been canceled without prejudice or disclaimer. Claims 7, 34, 35, as amended, and 38-40 do not recite "essentially identical." Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 3, 27, 29 and 32 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being vague. These claims have been canceled without prejudice or disclaimer.

In regard to the rejection described in the first paragraph on page 10 of the Office Communication, the claims have been amended to more definitely recite that the antibodies are to be cross-reactive against the gene delivery vehicle. Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection.

IV. 35 U.S.C. § 102

Claims 1-3, 5, 7-10, 13, 27-30, 34 and 36 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bramson *et al.* Claims 1-3, 5, 8-10, 13 and 27-33 and 36-37 have been canceled without prejudice or disclaimer. Therefore, the rejection directed to claims other than 7, 34 and 35 is considered moot.

Claim 7 now specifically recites "a human subject." Basis for the amendment can be found, for example, in paragraphs 22, 29 and 53.

Bramson *et al* does not anticipate claim 7, as amended, as each and every element of the claim is not taught by Bramson *et al.* Bramson *et al* disclose experiments in mice to determine if pre-existing anti-adenovirus antibodies (Ad-antibodies) would limit the effectiveness of subsequent gene therapy with adenovirus vectors. Because mice lack pre-existing Ad-antibodies, it was necessary to vaccinate the mice with a dose of adenovirus before the administration of the recombinant adenovirus gene-therapy vector. The results demonstrate that the recombinant adenovirus was still clinically effective despite the presence of Ad-antibodies in the treated mice.

The present invention provides the novel and inventive teaching that improves the administration of recombinant adenovirus to humans, by providing a human with antibodies reactive to the recombinant adenovirus gene-therapy vector, before the administration of said recombinant adenovirus. Bramson *et al* does not teach the person skilled in the art to actively provide humans with neutralizing adenovirus antibodies, because the experiments disclosed therein have been performed for a completely unrelated reason, and merely teaches that the inadvertedly present neutralizing Ad-antibodies in most humans do not prevent gene transfer into tumors (which is also described in the present specification, for example, in paragraphs 0023-0024). Thus, a person of ordinary skill in the art would not be motivated by Bramson *et al.* to actively induce the presence of neutralizing adenovirus antibodies in a human.

This conclusion is supported by the Office's position as stated on page 8 of the Office Communication. Specifically, that it was known in the art that the host immunity to adenoviral vectors is a barrier for successful gene therapy and the art known strategy is to use an alternative serotype to circumvent the neutralizing antibodies. The instant specification provides a new

concept that is contrary to the art known strategy. *Id.* Therefore, Bramson *et al.* does not anticipate the claims, as amended.

Furthermore, Bramson *et al.* observed that there appears to be less dissemination of the recombinant virus into peripheral organs when Ad-antibodies are present. This leads them to the suggestion that "**if organ toxicity is observed during the course of clinical trials**, it may be beneficial to immunize patients undergoing Ad-based therapies before the initiation of the clinical protocol" (page 1074, first column, line 3)(emphasis added). The invention is not limited to the instance where organ toxicity is observed during clinical trials: in fact, it teaches how to prevent such toxicity from the outset of the treatment, rather than act retrospectively when damage has already been done (see, for example, paragraph 0025 of the specification, described a tragic reason to start contemplating about possible improved adenovirus treatment regimes). Hence, the present invention claims providing the subject with antibodies directed to an adenovirus of the same serotype as the recombinant adenovirus containing the gene of interest in each and every instance where treatment with a recombinant adenovirus is done, *i.e.* irrespective of the presence or absence of other indicators. This means that all humans amenable to treatment with recombinant adenovirus could be treated according to the method of the invention.

Therefore, the applicants respectfully submit that the claims, as amended, are not anticipated by Bramson *et al.* Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 2, 5, 10, 13, and 28 have been canceled without prejudice or disclaimer. Thus, the rejections over Song *et al* and Russi *et al* are considered moot.

V. 35 U.S.C. § 103

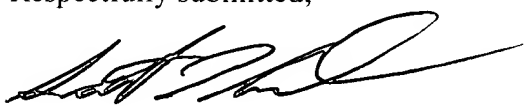
Claims 1, 2, 5, 31 and 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over Russi *et al.* in view of Esandi *et al.* Claims 1, 3 and 32 stand rejected under 35 U.S.C. § 103 as being unpatentable over Bramson *et al.* in view of Esandi *et al.*

Claims 1-3, 5, 31 and 32 have been canceled without prejudice or disclaimer. Thus, the rejections over Russi *et al.* in view of Esandi *et al.* and Bramson *et al.* in view of Esandi *et al.* are considered moot.

CONCLUSION

In the event questions remain after consideration of these remarks and amendments, the Office is kindly requested to contact applicant's attorney at the number given below.

Respectfully submitted,



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MARKED UP VERSION SHOWING CHANGES MADE

7. (Twice amended) A method for [delivering a gene of interest to a recipient cell in a host using a comprising a nucleic acid comprising said gene of interest, said method comprising:]

administering a recombinant adenoviruses containing a gene of interest to a human subject believed to be in need of said method, comprising providing a human subject with antibodies directed to an adenovirus of the same serotype or cross-reactive with the same serotype as the recombinant adenovirus containing the gene of interest, before administration of the recombinant adenovirus containing the gene of interest. [to a host a vaccine composition comprising a first gene delivery vehicle lacking said gene of interest;

allowing for a neutralizing humoral response to be raised by said host to said first gene delivery vehicle; and

administering a composition for gene therapy comprising a second gene delivery vehicle having a nucleic acid comprising said gene of interest in an amount greater than an amount which can be neutralized by said humoral response, said first gene delivery vehicle and said second gene delivery vehicle being cross-reactive].

34. (Amended) The method of claim [7] 38, wherein said [administering said composition for gene therapy] administration of the recombinant adenovirus containing the gene of interest occurs at least fourteen days after said [administering said vaccine composition] human subject is provided with antibodies directed to an adenovirus of the same serotype or cross-reactive with the same serotype as the recombinant adenovirus containing the gene of interest.

35. (Amended) The method of claim 7, further comprising [administering] providing a second dose of said antibodies directed to an adenovirus of the same serotype or cross-reactive with the same serotype as the recombinant adenovirus containing the gene of interest [vaccine composition] prior to said administrating said [composition for gene therapy] recombinant adenovirus containing the gene of interest.